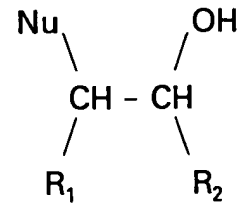


– wherein R_1 and R_2 form part of a cyclic moiety coupled to an organic or inorganic polymer optionally bearing functional -COOH or $-NH_2$ groups.

~~30~~. A support according to claim ~~29~~, wherein said cyclic moiety is a heterocycle.

~~31~~. A support according to claim ~~30~~, wherein said cyclic moiety is a ribose ring and Nu is the 2'-O function of said ribose ring protected with a protecting group.

~~32~~. A support according to claim ~~29~~, wherein Nu is a group of formula

REMARKS

The present claims are 19-32. The present claims represent subject matter of original claims 7-11, rewritten in order to more clearly define the instant invention; for example, as described in the specification at page 8, lines 21-26 and 32-37; page 9, lines 1-3; page 11, line 4-9; page 14, lines 5-11; and page 15, lines 14-16.

Applicants wish to thank examiner Crane for the courteous interview granted to their representative, on October 2, 1997. During the interview, all claims of record were discussed, along with the art cited in the Office action of record in the parent application. Other details of the interview are discussed, *infra*.

By the instant amendment, applicants are filing a new set of claims in order to define the invention more precisely and to more clearly distinguish the claimed invention from the prior art cited in the Office action. Former claims 7-11 have been redrafted as claim 19-33; in order to take into consideration the rejections of record in the parent case under 35 U.S.C. §112, second paragraph. Applicants respectfully submit that the instant amendment resolves the issues raised under the second paragraph of § 112.

In the parent application, claims were rejected under 35 U.S.C. 102 based on Vu, Lyttle, Webb et al. and Nelson et al.

Pursuant to the interview held with applicants' representative on October 2, 1997, and in view of the Interview Summary issued on even date, applicants understand that the Vu and Lyttle references cited in the statements of rejection no longer need to be considered. Indeed, as the examiner accurately pointed out in the Interview Summary, the publication dates of these references render the documents unavailable as prior art as a basis for valid rejections in view of the instant priority dates.

Therefore, the teachings of two references, Webb et al. and Nelson et al., remain relied upon by the examiner to support rejections of the claims under 35 U.S.C. §102(b). A brief discussion of the underlying principle of the present invention follows; to put the rejection in context.

The present invention concerns a support for the solid phase synthesis of nucleic acids. More particularly, the invention concerns a support which can be used irrespective of the first DNA or RNA nucleotide to be synthesized, and irrespective of the type of monomer reagent used during the synthesis (see page 5, lines 23-27 of the application as filed).

In this regard, a first important feature of the support of the present invention is that when using this support, all the nucleotides forming the particular nucleic acid to be synthesized, including the first nucleotide to be linked to the support, can be assembled using the same reaction conditions. Unlike many prior art processes, no particular conditions, different from those used to elongate the first nucleotide, are required in order to bind the first nucleotide on the support. As a consequence, the same monomer reagent can be used throughout the synthesis of the nucleic acid.

Another important feature of the present invention is the fact that once solid phase synthesis of an oligonucleotide is completed, only one reaction step is needed to both cleave the oligonucleotide from the solid support and generate a nucleotide sequence bearing a 3' terminal OH group. This is important as prior art supports usually require a first reaction step to remove the oligonucleotide from the support and a second reaction step to obtain an OH substituent at the 3' terminal nucleotide.

Therefore, in accordance with the present invention, the inventors have succeeded in designing a support containing reactive groups arranged in such a

manner that the following can be achieved when this support is used in solid phase nucleic acid synthesis:

- a protected 3' or 5' monomer reagent can be linked to the support **using the same conditions** as those for which the 3' or 5' end of the terminal nucleotide in the nucleic acid already synthesized are coupled with the 5' or 3' end of the next monomer reagent to be attached;
- once synthesis is terminated, cleavage of the oligonucleotide from the solid support can take place in a single reaction step in which the hydroxy group normally found at the 3' or 5' end of nucleic acids can be obtained.

These particular properties of the solid support of the invention have been achieved by linking - via covalent binding - a solid support, such as CPG, to a hydrocarbon radical comprising at least two reactive groups respectively located on first and second adjacent carbon atoms, which may be part of a cyclic moiety; said two reactive groups comprising:

- a hydroxy group capable of reacting selectively with the 3' or 5' phosphate, phosphite or phosphorothioate group of a first nucleotide monomer reagent to bind a first nucleotide monomer reagent to the hydrocarbon radical, under condensation conditions which are the same as those used to bind a second nucleotide monomer reagent to the first nucleotide monomer, and

- a nucleophilic group capable, after extension of the nucleic acid to be synthesized by successive incorporations of nucleotide monomer reagents to form a chain containing the first nucleotide monomer reagent as a first nucleotide monomer, of cleaving the 3' or 5' phosphate, phosphite or phosphorothioate group from the first nucleotide monomer through a one step β-elimination reaction, thereby removing the synthesized nucleic acid from the hydrocarbon radical which remains connected to the solid polymer and providing a hydroxy group on the 3' or 5' position of the first monomer.

It is to be noted that, when the first and second carbon atoms are part of a cyclic moiety, the hydrocarbon radical is not bound to the solid support through the first and second carbon atoms; rather, the hydrocarbon radical is linked to the support via covalent binding of the cyclic moiety to the support.

As demonstrated in the discussion below, it is respectfully submitted that none of the prior art documents cited in the Office action describe or suggest the specific combination claimed in the claims presently on file.

Webb describes a support for solid-phase oligonucleotide synthesis using a nucleoside linker. Among the various possible linker structures disclosed in this document, Webb et al. does not teach nor suggest the particular hydroxy-nucleophile combination set forth in the claims presently on file. Furthermore, Webb et al. is

completely silent on the particular interest of positioning these reactive groups on adjacent carbons.

However, it is precisely the proximity of these two reactive groups - on adjacent carbon atoms in the divalent radical - which allows the β-elimination reaction, which cleaves the phosphate group from the first nucleotide, to take place. It is submitted that the presence of such reactive groups on a support can not be reasonably inferred from Webb, which does not even refer to these reactions.

Another important issue to be raised concerning the Webb et al. reference is that, in accordance with the preferred embodiments of this document, the first nucleotide is attached to the support using reaction conditions which are substantially different from those under which the rest of the oligonucleotide is synthesized. This is readily illustrated by comparing the reaction conditions of Webb example 2, where the first nucleotide is bound to the linker, to those of Webb example 3, where the remaining portion of the oligonucleotide is synthesized under standard solid phase synthesis conditions.

Thus, the Webb et al. reference does not disclose or suggest a support presenting the features of the instant claims, as the reference is silent on at least the following important features of the support of the present invention:

- the **required presence of a hydroxy group** capable of reacting selectively with the 3' or 5' phosphate group of a first nucleotide monomer reagent

to bind the first nucleotide monomer reagent to the hydrocarbon radical, under condensation conditions which are the same as those used to bind a second nucleotide monomer reagent to the first nucleotide monomer;

- the required presence of the **combination** of **hydroxy** and **nucleophile** reactive groups;
- the required presence of the **specific hydroxy-nucleophile combination on adjacent carbons** which allows, after synthesis of the desired nucleic acid, cleavage of the 3' or 5' phosphate group from the first nucleotide monomer through a one step β-elimination reaction to simultaneously remove the nucleic acid from the hydrocarbon radical which remains bound to the solid support and to provide a hydroxy group on the 3' or 5' position of the first monomer.

Hence, it is respectfully submitted that the invention as presently claimed in the claims on file is novel and unobvious over Webb et al.

Nelson et al. generally concerns a support reagent useful in solid phase oligonucleotide synthesis. More particularly, Nelson concerns covalently attaching labels and reporter molecules to oligonucleotides during solid phase synthesis (Nelson, page 7187). The support proposed by Nelson has been designed for the specific purpose of synthesizing oligonucleotides comprising functional groups or labels not normally found in nucleic acid sequences.

With reference Figure 1 of Nelson (page 7188), to which the examiner specifically refers at page 8 of the Office action, and the structure labeled "MF-CPG," it is submitted that this structure does not anticipate or render obvious the invention described in the instant claims. Indeed, this structure is chemically different from those claimed in the present application not used in the same context as the present invention and does not allow the person skilled in the art to achieve the same results.

As discussed previously, prior art techniques available for solid phase oligonucleotide synthesis usually make use of supports to which the first nucleotide is pre-attached under reaction conditions which are different from those encountered during the actual elongation phase of the oligonucleotide.

The structure of Figure 1 of Nelson et al. replaces a nucleotide which is **pre-attached** on a solid support with a primary aliphatic amine which is in turn transferred to the 3' terminus of the synthesized oligonucleotide. This is discussed in detail beginning at page 7187 of the reference. According to the reference, in conventional solid phase DNA synthesis, the 3' terminal nucleotide is pre-attached to the CPG support from the 3' hydroxyl through a succinimic acid linking arm, and the oligonucleotide is synthesized from the 5' hydroxyl repetitive cycles of chemical reactions. Nelson (page 7187, last incomplete paragraph) newly reports

> the synthesis and use of a novel multifunctional controlled pore glass, MF-CPG® (Fig. 1), which introduces an aliphatic primary amine to the 3' terminus of an oligonucleotide via solid phase synthesis.

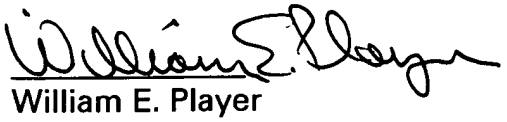
Hence, the oligonucleotides obtained with the support described in Nelson et al. invariably bear an additional functional group at their 3' terminus. It submitted that, in this regard, the teachings of Nelson et al. do not suggest nor disclose the invention claimed in the present application; the structure of Nelson et al. does not allow the synthesis of unmodified oligonucleotides, that is, oligonucleotides bearing an OH group at their 3' terminus.

The teachings of Nelson et al. are clearly different from those of the present invention claimed, in which the claimed support allows the oligonucleotide to completely removed from the linker while providing an OH group at the 3' end of the oligonucleotide. Indeed, the nature and structural arrangement of the support of the present invention is such that the specific hydroxy-nucleophile combination on adjacent carbons allows, after synthesis of the desired nucleic acid, cleavage of the 3' or 5' phosphate group from the first nucleotide monomer through a one step β-elimination reaction to (i) remove the nucleic acid from the hydrocarbon radical and (ii) provide a hydroxy group on the 3' or 5' position of the first monomer.

It is therefore respectfully requested that the claims of record are patentable over Nelson et al.

Favorable action commensurate with the foregoing is requested.

Respectfully submitted,

By: 
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